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(54) Title: NOVEL NATURAL POLYMER-BASED MATERIAL WITH IMPROVED PROPERTIES FOR USE IN HUMAN AND VETERINARY MEDICINE AND THE METHOD OF MANUFACTURING SUCH

(57) Abstract: The invention is concerned with novel natural polymer-based material and preferably collagen-based material with improved mechanical, physical, functional and handling properties for use in human and veterinary medicine in both in vivo and in vitro condition, wherein the material is a natural polymer, preferably collagen, of animal or/and human or/and recombinant or/and transgenic origin optionally additionally containing biologically active substances such as hemostatic agents, growth factors, cytokines, hormones, drugs and the like, and/or biologically important and tissue-compatible inorganic or/and organic substances or/and their derivatives which can improve the mechanical, functional and handling properties. This novel material is obtainable by simultaneous heat and pressure treatment of a basic natural polymer material. Such process for the manufacture of the novel material is a further subject of the present invention.

Novel Natural Polymer-Based Material with Improved Properties for Use in Human and Veterinary Medicine and the Method of Manufacturing such

Description

The present invention relates to novel natural polymer-based material with improved mechanical, physical, functional and handling properties for use in human and veterinary medicine in both in vivo and in vitro condition and to methods for the manufacture of such material.

The use of various different xenogenous, allogenic or autologous collagen-based materials in human and veterinary medicine in both experimental (i.e. ex vivo) and in vivo condition is known. Such a collagen material may be used for example as hemostatic agent, as substitute of missing tissue, as skin equivalent, as material for tissue augmentation or as a carrier for biologically active substances or drugs.

Purified allogenic or xenogenous collagen is almost fully biocompatible with human collagenous and connective tissue and may be incorporated into and/or subsequently remodeled to a host tissue without foreign body reaction and immunologic rejection.

If used as a hemostatic agent, collagen-based material must have both biological and mechanical features promoting hemostasis, i.e., intact collagen fibers and an optimal porosity.
If used as tissue substitute (equivalent), the collagen-based material must have optimal matrix properties promoting formation of granulation tissue, angiogenesis, vascularization and epithelization.
If used as a carrier of biologically active substances, the collagen-based material must have features allowing an optimal release of incorporated agent(s) as well as good matrix properties.

In all cases, however, the handling of the collagen-based material, its mechanical stability, flexibility and, if necessary, the ability to be sutured or sealed are important factors characterizing a good, ready-to-use and user-friendly material.

The most popular commercially available collagen-based materials are sponges, membranes or injectable solutions of various fibril contents and viscosity.
For hemostasis, tissue substitution and as a carrier for biologically active substances both lyophilized collagen-based sponges and/or air-dried membranes are the most popular.
All these known materials, however, are not stable enough to be sutured, rolled, screwed or sticked, or to be used in areas of mechanical tension.

To improve the mechanical properties of such collagen materials, different additional crosslinking procedures have been developed. The most popular are: chemical crosslinking (i.e. with aldehydes) or physical crosslinking (i.e. dehydro-thermal treatment).
The aldehyde-based crosslinking may negatively influence the biocompatibility of collagen and may lead to some residues of aldehydes (or its derivatives) in the final product.
The dehydro-thermal treatment, which is used mostly for collagen sponges, has also its natural limitation and does not lead to materials with sufficiently improved properties.

To overcome these problems different alternative manufacturing processes have been described.

The US-Patent 4,655,980 describes the possible manufacturing of a collagen membrane based on a soluble collagen gel suspension. The membrane may be obtained by applying pressure to the gel, or by

disrupting the gel and separating the resulting precipitate for casting. Depending on the dimension and shape of the casting mold, either a membrane or solid can be obtained. In fact, the manufacturing of such membrane is based on a commercially available soluble, injectable, atelocollagen product of Collagen Aesthetics, Paolo Alto, CA, USA.

The US-Patent 5,219,576 describes a collagen implant material useful as wound healing matrices and delivery system for bioactive agents. Beside manufacturing traditional collagen sponges based on casting and drying of a soluble collagen gel suspension, the patent describes the manufacturing of multilayer material by casting and freezing the individual layers and then lyophilizing the entire composite at once. A possibility of additional crosslinking by both aldehyde and dehydro-thermal processing of the final product is also discussed.

The US-Patent 4,522,753 describes, for example, a method for preserving porosity and improving stability of collagen sponges by both aldehyde and dehydro-thermal treatment. The negative pressure (vacuum) used may vary from about 1 mtorr up to slight vacuum just below atmospheric pressure.

The US-Patent 4,578,067 describes a hemostatic-adhesive collagen dressing in form of dry-laid, non-woven, self-supporting webs of collagen fibers. The manufacturing of such material is based on a Rando-feeder and Rando-webber techniques. The collagen fibers from the Rando-feeder are introduced into the air stream of the Rando-webber and form a fiber mass of uniform density. Such mass may then be processed by pressing or embossing or by calendering at a temperature ranging from room temperature to 95°C.

The US-Patent 5,206,028 describes a collagen membrane having improved physical and biological properties. Such membrane does not

swell appreciably upon being wetted and maintains its density. The manufacturing of such translucent, collagen Type-I based material is based on compression of collagen sponges in a roller press with a calibrate aperture followed by aldehyde cross-linking. For additional mechanical stabilization, the cross-linked membrane may be re-wetted, re-lyophilized and pressed again under standard conditions.

The US-Patent 4,948,540 describes a mechanically stable, comfortable collagen wound dressing sheet material fabricated by lyophilizing a collagen composition (soluble and insoluble collagen parts in range of 1:20 to 10:1) and compressing the porous pad at a pressure between about 15,000 and 30,000 p.s.i. The material may be also cross-linked by dehydro-thermal treatment to improve mechanical stability.

At present, all of the methods for manufacturing of collagen-based material with improved mechanical, physical and biological properties (as described above) are not in use for industrial manufacturing of collagen-based material.

There is a need, however, both in human and veterinary medicine, to use and introduce an industrially manufactured, ready-to-use, customer friendly collagen-based material or materials based on other natural polymer showing similar properties which will be fully biocompatible, mechanically stabile, flexible, easy-to-handle, and which can be sutured or/and sealed, rolled or/and screwed, cut or/and meshed.

Moreover, it would be of advantage, if such material could contain biologically active substances or/and agents, e.g., to promote healing or to protect from (or cure) infections.

The most important, however, the new product has to be easy to manufacture and not expensive.

An object of the present invention, therefore, was to create a novel natural polymer-based product with improved mechanical and/or physical and/or bio-physiological properties which can be easily manufactured by industrial methods.

Moreover, a further object of the present invention was to create a material with novel mechanical and/or physical and/or bio-physiological properties which allows the successful use of the material in areas and/or indications in which such properties are necessary.

These objects are solved according to the invention by providing a natural polymer-based material with improved mechanical, physical and handling properties for use in human and veterinary medicine in both invivo and in vitro condition wherein the material is a collagen of animal or/and human or/and recombinant or/and transgenic origin optionally containing additionally

a) biologically active substances such as hemostatic agents, growth factors, cytokines, hormones, drugs (like for example antibiotics, anti-inflammatory agents) etc,

and/or

b) biologically important and tissue-compatible inorganic or/and organic substances or/and their derivatives which can improve the mechanical, functional, biological and handling properties of the material,

wherein the material is obtainable by simultaneously treating the basic natural polymer material with defined heat and defined pressure and, if applicable, adding the additional biological substance(s) of a) and/or b) to the basic collagen material prior or subsequent to the heat and pressure treatment.

The term "natural polymers", according to the invention, defines substances that show properties similar to collagen and which can be used for the same applications as collagen.

Examples of substances which are encompassed by the term are collagen itself, but also gelatine, a collagenous product, and hyaluronic acid.

According to the invention all of these materials can be used as basic materials for the production of the material of the invention, although collagen is the most preferred material used.

Although in the following collagen is described as basic material, within the framework of the invention it is to be understood that the same description of manufacture and properties of the final product also applies to other natural polymers which satisfy the above definition.

According to the invention, defined mechanical pressure and defined heat are applied in a way which protects the fibrils (native and/or renaturate) of the collagen or the other natural polymers from degradation or/and denaturation or/and melting and which save the natural biological properties of collagen (i.e. hemostatic properties or matrix properties). Moreover, the method by which the collagen-based material of the invention is prepared, allows to create and manufacture collagen-based material with improved mechanical properties like stability, dry and wet tension, suturing abilities, improved flexibility, with excellent hemostatic properties, improved wetting abilities, improved absorption of water or/and other physiologic fluids and which can be rolled or/and screwed in both dry and wet condition, and which can be cut or meshed without loosing shape and basic properties.

Moreover, the present invention allows the manufacturing of collagen-based products which may contain biologically active agents and/or inorganic or/and organic substances of the kind as described above and which can additionally serve as a carrier for living cells, tissue sealant, etc.

The present invention opens new possibilities for the use of collagen-based materials in those areas of the human or animal body or in those in vivo and ex vivo indications in which the use of such biological material was previously not possible or applicable due to, i.e., insufficient mechanical properties.

The manufacturing steps used for the preparation of the material and described in the present invention can be easily incorporated into a routine manufacturing process and allow to save time and costs if compared to other currently used methods (see above).

The use of defined mechanical pressure for industrial manufacture of collagen membrane-like products based on freeze-dried collagen sponges containing active substances, i.e., antibiotics (i.e. gentamicin) is known per se (i.e. EP 0069260, issued 09/25/1985, owned by Syntacoll AG, Herisau, Switzerland).

The influence of a moderate heat, especially if used together with a negative pressure (vacuum), for induction of additional cross-linking sites in collagen sponges has been described previously as dehydro-thermal-treatment (see above).

The present invention now combines heat and positive pressure (mechanical pressure) for the treatment of the basic materials according to the invention, which has never been proposed in the state of the art, but leads to products with highly unexpected, superior properties as described above.

The collagen used for manufacture of the improved collagen-based material of the invention may be either of animal origin (xenogenous) or human (autologous or allogenic) origin or may be obtained from genetically manipulated organisms (recombinant techniques or transgenic

organisms) which can produce recombinant or transgenic proteins, or can be obtained by other techniques of genetic engineering, equivalent or similar.

The collagen material used for manufacturing of the improved collagen-based material may consist of various known collagen types (preferentially of at least one or/and or all of the following: Typ-I, -II, III, IV, VII, IX alone or in a mixture). The most important collagen in the human and animal body is the Typ-I collagen. This material can be easily obtained for example from animal tissue (skin, tendons, etc.,) by industrial methods according to state-of-the-art, GMP-conformed techniques.
Both enzymatically treated or not enzymatically treated collagen can be used for manufacture. If treated with proteolytic enzymes, non-helical parts of the collagen molecule will be separated from the triple-helical collagen chain(s) (atelocollagen).

The basis material for manufacturing an improved collagen-based material is a collagen sponge. The basis for such material may be collagen dispersion and/or suspension (i.e. in water or other non-organic solvent) of 0.5 to 5.0 weight% of dry collagen. A sponge of defined porosity may be obtained by freeze-drying. The collagen sponge may be manufactured using various state-of-the-art techniques.

To improve mechanical properties, handling and to achieve new features of the collagen-based material collagen sponges with various different, but defined water (solvent) contents will be treated simultaneously with defined continuos heat and defined continuos mechanical pressure for a defined period of time.

Preferably, according to the present invention, the water or solvent content ranges from 2 % to 40 % of weight.

The temperature used preferably lies within the range of from 50 °C to 200 °C.

The pressure used preferably lies in the range of from 0,5 kg/cm² to 1000 kg/cm².

The time period for the heat and pressure treatment preferably lies within the range of from 0.1 second to 1 hour.

As a result of such treatment according to the invention, a collagen-based sponge will be pressed to a membrane-like structure. This product has excellent hemostatic properties, excellent and improved absorbing capacity, excellent and improved mechanical properties (rolling, screwing, suturing, etc.,).

Moreover, such a product shows much better handling properties than other known collagen based products such as freeze-dried sponges or air-dried membranes.
Additionally, the new properties of such material allow its use in those anatomic sites or medical indications, in which the use of traditional collagen-based sponges or membrane was hithero not possible or not practicable.
Moreover, the new properties of the material of the invention allow the use of sutures or other methods of mechanical fixation in situ, which was not possible in the case of traditional collagen-based materials.

The final product according to the present invention may be packed using any suitable packaging and end-sterilized by, i.e., ethylene oxide vapors, gamma radiation, electron beam radiation or any other sterilization procedure suitable for such material.

Another subject of the present invention is a process for the manufacture of a collagen based material having improved mechanical and/or physical, and/or functional and/or handling properties for use in human and veterinary medicine in both in vivo and in vitro condition and described above in more detail, by simultaneously treating a basic collagen material with defined heat and defined pressure.

The manufacturing of the novel collagen-based material is easy and can be incorporated into standard industrial production lines. The necessary equipment is commercially available.

For the process according to the invention, as basic collagen material preferably a sponge or a membrane made from a dispersion or/and suspension with a collagen content of 0.5 to 5 weight% is used.
In further preferred embodiments of the invention, the temperature used for the heat treatment lies within the range of from 50 to 200 °C and the pressure used for the pressure treatment lies within the range of from 0,5 to 1000 kg/cm^2. Preferably the treatment time lies within 0.1 second to 1 hour.

The following examples are intended to further illustrate the invention.

Example 1

Manufacturing of a novel collagen-based membrane-like material

A freeze-dried collagen sponge, like i.e. Collatamp® (manufacturer: SYNTACOLL AG, Herisau, Switzerland) with a thickness of 5 mm and a collagen content of 5,6 mg/cm^3 is conditioned in a moisture chamber to a water content of 14 % of weight.
After conditioning, defined mechanical pressure and defined heat are applied simultaneously to the sponge using an appropriate press.

The pressure of 5 kg/cm² is applied continuously to both sites of the sponge for a time period of 10 seconds; the temperature of pre-heated press surfaces is 80°C and remains constant during pressing.
After such thermal pressing procedure (ThermPress™), the resulting paper-like collagen-membrane has a thickness of 0,1 mm.
Physical properties of the new created product are markedly improved, if compared to a standard collagen sponge: (1) the product is easy to handle and may be rolled or screwed without breaking, (2) the swelling time of the product is dramatically reduced, (3) the absorption of fluids increases, (3) the wet product (after fluid absorption and/or swelling) remains very flexible, (4) the wet product has much better elasticity and excellent wet tensile strength.

The novel features of the product make it very interesting for use in general surgery, vascular surgery, neurology and neurosurgery, orthopedics and orthopedic surgery, cardiosurgery, gynecologic surgery, ophthalmology, laryngology, and in all other medical and veterinary disciplines including wound healing and burns.
Moreover, the novel product may have benefit if used as a tissue substitute or as a matrix for cell growth especially in tissue engineering and creation of artificial organs.

Example 2

Manufacturing of a novel collagen-sheet with improved swelling properties

A freeze-dried collagen-based sponge (collagen content 30 mg/cm³) with a thickness of 5 mm is conditioned in a moisture chamber to have a water content of 14% of weight.

After conditioning, pressure and heat are applied simultaneously to the sponge.

The pressure of 5 kg/cm² is applied from both sides of the sponge for a time of 10 seconds. The temperature of pre-heated press surfaces is 80°C and remains constant during pressing.

After such a thermal pressing procedure (ThermPress™), the resulting collagen sheet is 0,6 mm thick and had the appearance of a strong paper or is leather-like. If compared to standard freeze-dried collagen sponge, such collagen sheet has dramatically improved swelling properties. Moreover, the swelling time is markedly reduced and fluid binding capacity is increased.

Such collagen sheet can swell to 30 times it's weight in maximal time of 10 seconds. Additionally, hemostatic properties are markedly increased. In swollen condition the collagen sheet is mechanical stable and has a high wet tensile strength. Both the dry and the wet sheet is very easy to handle, can be cut to any desired or suitable form. Due to its high stiffness and high elasticity, it is more easy to apply it to different locations in the body.

The novel features of this product make it very interesting especially for use in hemostasis (properties much better than all standard hemostatic agents as e.g. standard collagen sponge, gelatin sponge, regenerating cellulose, cotton gaze, etc.). Moreover, the product may have benefits in general surgery, vascular surgery, neurology and neurosurgery, orthopedics and orthopedic surgery, cardiosurgery, gynecologic surgery, ophthalmology, laryngology, and in all other medical and veterinary disciplines including wound healing and burns.

Moreover, the novel product may have benefit if used as a tissue substitute or as a matrix for cell growth, especially in tissue engineering and creation of artificial organs.

Additionally the novel product may be use as a carrier for biologically active substances as i.e. growth factors, cytokines, hormones, drugs,

etc., which can be added ex tempore and/or incorporated to the product by absorption.

As the basic collagen sponge used for thermal press procedure can contain biologically active substances as i.e. growth factors, cytokines, hormones, drugs, etc., novel product created by the method described by the present invention can also contain such substances. However, in such cases the manufacturing condition have to be adapted to save the biologic activity of the particular additive.

Claims

1. Natural polymer-based material with improved mechanical, physical, functional and handling properties for use in human and veterinary medicine in both in vivo and in vitro condition and wherein
the material is a natural polymer of animal, or/and human or/and recombinant or/and transgenic origin optionally containing additionally
   (a) biologically active substances such as hemostatic agents, growth factors, cytokines, hormones, drugs (such as antibiotics, anti-inflammatory agents) etc.,
   and/or
   (b) biologically important and tissue-compatible inorganic or/and organic substances or/and their derivatives which can improve the mechanical, functional, biological, and handling properties of the material,
obtainable by simultaneously treating a basic natural polymer material with defined heat and defined pressure, and, if applicable, adding the additional biological substance(s) of a) and/or b) to the basic collagen material prior or subsequent to the heat and pressure treatment.

2. Natural polymer-based material according to claim 1, wherein the natural polymer is collagen.

3. Natural polymer-based material according to claim 1 or 2, wherein the basic material used for manufacturing the final product is a sponge or a membrane made from a dispersion or/and suspension of 0.5 – 5 weight% of natural polymer, preferably collagen.

4. Natural polymer-based material according to claim 1, 2 or 3, wherein the heat conditions used comprise a temperature in the range of from 50 to 200°C.

5. Natural polymer-based material according to anyone of claims 1 to 4, wherein the pressure conditions used comprise a pressure of between 0,5 and 1000 kg/cm².

6. Natural polymer-based material according to anyone of claims 1 to 5, wherein the time of simultaneous application of the continuos heat and pressure lies within 0.1 second and 1 hour.

7. Process for the manufacture of a natural polymer-based material according to anyone of claims 1 to 6, characterized by simultaneously treating a basic natural polymer material with defined heat and defined pressure.

8. Process according to claim 7, wherein the basic natural polymer material is collagen.

9. Process according to claim 7 or 8, wherein the basic natural polymer material used is a sponge or a membrane made from a dispersion or/and suspension of 0.5 to 5 weight% of natural polymer, preferably collagen.

10. Process according to claim 6, 7 or 8, wherein the heat conditions used comprise a temperature in the range of from 50 to 200°C.

11. Process according to anyone of claims 7 to 10, wherein the pressure conditions used comprise a pressure of between 0.5 and 1000 kg/cm².

12. Process according to anyone of claims 7 to 11, wherein the time of simultaneous application of continous heat and pressure lies within 0.5 seconds and 1 hour.

INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L15/32 A61F13/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, EPO-Internal, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 578 067 A (CRUZ JR MAMERTO M) 25 March 1986 (1986-03-25) column 9, line 32 -column 10, line 30; claims; tables 4,5 ---	1,2,4, 6-8, 10-12
X	DE 28 43 963 A (MERCK PATENT GMBH) 24 April 1980 (1980-04-24) page 6, line 5 - line 17; claims page 7 page 10, line 26 - line 34 page 11 -page 14 page 15, line 12 - line 31; example 4 --- -/--	1,2,4-8, 10-12

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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